Table 404-5 Subject Exclusions

	Placebo N = 148	Estrostep® N = 147
Excluded From MITT Population for:		
No Study Medication	0	0
Excluded From ITT Population for:		
No Baseline Assessment Data	1	1
Excluded From Per-Protocol Population for:	**(still included in ITT)**	
Lesion Counts Were too High at Screening	2	3
Lesion Counts Were too Low at Screening	3	2
Inadequate Washout	3	0
Withdrawn Before Cycle 3	20	22
Non-compliant With Study Medication During Last 3 Cycles	4	4
Substantial use of Prohibited Concurrent Medications	3	5

Reference: Appendix A.6 and C.5

a: from Appendix C.4

Table 404-6 Reasons for patient withdrawal from the study

	Placebo	Estrostep®
Lack of efficacy	1	
Withdrew consent	9	6
Moved away	4	4
Lost to follow up	5	4
Scheduling difficulty		1
Sponsor requested termination	3	1
Error in dispensed medication. Number re-assigned	1	

From Appendix C.4, Table 3 page 33, vol 16 and from Response to additional data request, supplied by sponsor in submission 2000-12-20A

*sponsor submitted greater detail about patients terminated for administrative reasons, as shown later on Table S-7 and Table S-8, on pages 52 and 53

From Response to additional data request, supplied by sponsor in submission 2000-12-20A

Reviewer comment: the number of subject withdrawals for each category was not dissimilar for both active and placebo, suggesting subjects did not experience a significant effect difference

Table 404-7 Reported number of subjects compliant with treatment by cycle

Intent-to-Treat Population	Placebo (N=147)	Estrostep® (N=146)
Cycle 2 (V-4)	125	122
Cycle 3 (V-5)	120	116
Cycle 4 (V-6)	111	113
Cycle 5 (V-7)	106	112
Cycle 6 (V-10)	101	110
Per Protocol Population	Placebo (N=112)	Estrostep® (N=110)
Cycle 2 (V-4)	111	108
Cycle 3 (V-5)	111	106
Cycle 4 (V-6)	103	105
Cycle 5 (V-7)	99	104
Cycle 6 (V-10)	94	102

Reviewer comment: the differences in compliance between active and placebo are very small, perhaps suggesting that the difference in effectiveness felt by subjects was not great

Prior medications

The treatment groups were balanced with respect to prior medications. The most frequently used medications prior to study in the Estrostep® group were ibuprofen (9%), [redacted] and

acetylsalicylic acid (3%) and in the placebo group were ibuprofen (7%), [redacted] tretinoin (2%), and fluconazole (2%). Tretinoin was used by 1% of the Estrostep-treated subjects. A complete summary of prior medications is located in Appendix C.7.1 for the ITT population and in Appendix C.7.2 for the per-protocol

Concurrent Medications:

Table 404-8 Most Frequently Used Concurrent Medications —Intent-to-Treat Population

Medication	Placebo N = 147	Estrostep N = 146
[redacted]		
Multivitamins	19 (13%)	19 (13%)
Ibuprofen	18 (12%)	13 (9%)
Ascorbic acid	10 (7%)	8 (5%)
Acetylsalicyclic acid	7 (5%)	5 (3%)
Pseudophedrine hydrochloride	5 (3%)	7 (5%)

Reviewer's comment: although these were the single most common concurrent medications, many subjects took antibiotics and many subjects took a variety of non-steroidal anti inflammatories for various lengths of time. This was true also for study 403

EFFICACY

Endpoints and analysis

The same criteria as for 403 were used for 404

The following analyses were discussed and concurred between the clinical and statistical reviewers. The supporting efficacy endpoint result are fully explained in the statistical review and will not be repeated here .

The following table summarizes the efficacy data from the statistics review

Table 404-9. Summary of analysis of effectiveness of Estrostep over placebo

404	Per Protocol N= 110 Estrostep® / 102 Placebo				ITT N=146 Estrostep® / 147 Placebo			
Evaluation ▸	Mean of % reduction From baseline		Mean change from baseline		Mean of % reduction From baseline		Mean change from baseline	
Lesion Type ▾	%	p	N	p	%	p	N	P
Inflammatory	15.2	.0001	4.7	.0001	12.6	.0022	3.5	.0082
Baseline mean			30/29				30/29	
Comedones	19.7	.0012	7.5	.0001	15.7	.0038	6.2	.0019
Baseline mean			40/42				41/40	
Total	17.7	.0001	12.2	.0001	14.5	.0002	9.7	.0004
Baseline mean			70/71				70/69	
% Minimal or Better	11.9% 22%/ 10%	.009			11.1% 19%/ 7%	.012		

Reviewer comment: In study 404, the Estrostep® group demonstrated, in the Intent-To-Treat population, a statistically significant decrease in Total lesion counts as well as for comedones and for inflammatory. At the end of the study, the difference from baseline over placebo was 3 for total lesion counts, 6 for comedones, and 9 for inflammatory lesions. In this study, the results obtained in the PP population were supportive of efficacy but of similarly lacking in robustness. The mean of the percent reduction of lesions from baseline was statistically significant for total lesion counts, for comedones and for inflammatory lesions, and the differences between Estrostep® and placebo ranged 12% to 14%. For the PP population, the range was similar, 15-19%.

In the per-protocol subjects, for inflammatory lesions and for total lesions the interaction was clearly quantitative, as it was in the ITT population for total lesions. Estrostep® was generally equal to or superior to placebo, but the degree of superiority varied considerably across centers. In all cases, the effect size for this interaction was considerably less than the test for differences in treatment. For inflammatory lesions in the ITT population, the mean differences were larger, but so was the amount of variation, so that the actual effect size is less than for the per protocol population. Similarly the interactions for percent change from baseline in inflammatory lesions seem to be quantitative. The presence of some quantitative interaction is tentatively ascribed to an artifact of the experiment

On Facial Global Assessment, the percent of Estrostep® treated subjects (19%) who were graded as "absent and/or minimal" at study end was statistically significantly different from the placebo-treated group (7%). The difference over placebo at study end was 11%.

Safety

There were no deaths or SAEs in either treatment group.

Overall, there were no unexpected differences between treatment groups in AEs and associated AEs (Appendix C.27). One hundred and two (69%) Estrostep® subjects and 92 (62%) placebo subjects experienced an adverse event. Fifty-nine (40%) of the Estrostep® subjects and 28 (19%) of the placebo subjects had an associated AE.

Metrorrhagia, infection and headache were the most frequently reported AES. Some AEs usually associated with oral contraceptives i.e.: breast pain, metrorrhagia and moniliasis were more common among Estrostep-treated subjects.

Unintended pregnancy (5 placebo-treated subjects and 1 Estrostep-treated subject) was captured on an AE CRF for tracking purposes, but was not considered an AE for this study

Table 404-10 Overview of Adverse Events—Randomized Subjects

	Placebo N (%)	Estrostep® N (%)
Subjects with AEs		
All	92 (62%)	102 (69%)
Associated	28 (19%)	59 (40%)
AEs by Maximum Intensity		
Mild	37 (40%)	45 (44%)
Moderate	41 (45%)	46 (45%)
Severe	11 (12%)	10 (10%)
Missing	3 (3%)	1 (1%)
SAEs		
All	0	0
Deaths	0	0
Withdrawals due to AEs		
All [a]	3 (3%)	7 (5%)
Associated	2 (1%)	7 (5%)

[a]: Six additional withdrawals (5 placebo, 1 Estrostep) were due to unintended pregnancy, which sponsor does not considered an AE (Appendix: C.26)

Table 404-11 Most Frequently (>5%) Occurring All and Associated Adverse Events —Randomized Subjects

Adverse Event	Placebo N (%)		Estrostep® N (%)	
	All	Associated	All	Associated
Metrorrhagia [a]	5 (3%)	5 (3%)	40 (27%)	38 (26%)
Infection	21 (14%)	0	24 (16%)	0
Headache	23 (16%)	11 (7%)	11 (7%)	7 (5%)
Flu Syndrome	9 (6%)	0	7 (5%)	0
Pharyngitis	9 (6%)	0	7 (5%)	0
Abdominal Pain	3 (2%)	0	8 (5%)	2 (1%)
Sinusitis	2 (1%)	0	8 (5%)	0
Nausea	7 (5%)	4 (3%)	7 (5%)	5 (3%)
Dysmenorrhea	6 (4%)	0	7 (5%)	1 (1%)

[a] One case of metrorrhagia, included here, was miscoded to hemorrhage under the cardiovascular system on the AE Appendices. Appendix C.27

Adverse Events by Intensity

Most AEs were moderate or mild in intensity (Appendices C.29 and C.30). Less than 13% of subjects in either treatment group had AEs considered severe. No unexpected differences between treatment groups were found. The only severe AEs with more than 1 occurrence were flu syndrome, headache and pain; flu syndrome and headache each occurred 3 times in the placebo-treated group and pain occurred twice in the placebo group.

Withdrawals Due to Adverse Events

There were no unexpected differences between treatment groups in AEs resulting in withdrawals (Appendix C.33). Overall, 10 subjects withdrew from study due to an AE (Table 15). Seven (5%) subjects in the Estrostep® group and 3 (2%) in the placebo group withdrew due to an AE. Breast pain, metrorrhagia and vaginal hemorrhage were the most frequently reported reasons for withdrawal due to an AE among Estrostep-treated subjects; each of these caused 2 withdrawals

from the study in the Estrostep-treated group. The narratives for all subjects who withdrew due to an AE are located in Appendix B.3.2.

Table 404-12 Withdrawals Due to All and Drug-Related Adverse Events

Adverse Event	Treatment	Subject No.	Study Day of Onset /Resolution	Outcome[a]	Drug-Related
Abnormal Vision	Placebo	010-426	8/cont	Not yet recovered	No
Breast Pain	Estrostep	009-257	Unk/unk	Unkown	Unknown
Breast Pain	Estrostep	010-461	1/cont	Not yet recovered	Yes
Emotional Lability	Placebo	005-041	68/75	Recovered	Yes
Flatulence	Estrostep	010-461	1/cont	Not yet recovered	Yes
Headache	Placebo	009-020	Unk/unk	Unknown	Yes
Metrorrhagia	Estrostep	011-516	16/cont	Not yet recovered	Yes
Metrorrhagia	Estrostep	014-420	7/cont	Not yet recovered	Yes
Migraine	Estrostep	005-298	1/cont	Not yet recovered	Unknown
Nausea	Placebo	009-020	Unk/unk	Unknown	Yes
Nausea	Estrostep	010-461	1/cont	Not yet Recovered	Yes
Vaginal Hemorrhage	Estrostep	014-406	1/30	Recovered	Yes
Vaginal Hemorrhage	Estrostep	017-470	96/104	Recovered	Yes
Weight Gain	Estrostep	009-257	Unk/cont	Not yet Recovered	Unknown
Weight Gain	Placebo	005-041	46/cont	Not yet Recovered	Yes

[a] At subject withdrawal Cont. = continued Unk. = unknown Appendices B.3.2, C.33, and F.2

Reviewer comment: most adverse events linked with Estrostep® had either unknown outcome or not yet recovered outcome, suggesting that either the adverse events were prolonged or follow up was very short

Withdrawals Due to Adverse Events (376-404 Appendix B.3.2)

Subject 041 at Site 005, (Protocol 376-404), a 19-year-old white female with no significant medical history, was randomized to placebo. The subject experienced weight gain on Day 46 and mood swings on Day 68. The mood swings resolved on Day 75 and the study medication was discontinued on Day 78. The investigator considered these events to be related to the study medication.

Subject 298 at Site 005, (Protocol 376-404), a 16-year-old white female with a history of migraine headaches, insomnia, and depression, was randomized to Estrostep. Starting on Day 1 the subject experienced multiple episodes of migraine headaches. The recurring headaches were treated with ibuprofen and acetaminophen starting on Day 28. Study medication was discontinued on Day 69 and a final visit occurred on Day 71.

Subject 020 at Site 009, (Protocol 376-404), a 28-year-old white female with a history of occasional headaches, was randomized to placebo. On an unknown date, the subject experienced nausea and headache. The date of study medication discontinuation is also unknown. Concomitant medications included phentermine, pseudoephedrine hydrochloride, and ibuprofen. The investigator considered these events to be related to the study medication.

Subject 257 at Site 009, (Protocol 376-404), a 28-year-old black female with no significant medical history, was randomized to Estrostep. The subject reported weight gain and breast discomfort at Day 78 and study medication was discontinued on an unknown date as a result of these events. The investigator recorded the relationship of these events to the study

medication as unknown.

Subject 426 at Site 010, (Protocol 376-404), a 31-year-old Asian/Pacific Islander female with no significant medical history, was randomized to placebo. The subject developed decreased visual bilateral acuity on Day 8 and study medication was discontinued on Day 11. The final study visit occurred on Day 22 and the subject was to be followed by her eye doctor. Concomitant medications included vitamin E, aspirin, and clindamycin HCl vaginal cream. The investigator considered this event not related to the study medication.

Subject 461 at Site 010, (Protocol 376-404), a 31-year-old white female with a history of uterine fibroids, was randomized to Estrostep. The subject developed abdominal bloating, nausea, and breast tenderness on Day 1 and study medication was discontinued. The investigator considered these events to be related to the study medication.

Subject 516 at Site 011, (Protocol 376-404), a 16-year-old Asian/Pacific Islander female with no significant medical history, was randomized to Estrostep. The subject developed irregular menstrual bleeding on Day 16 and study medication was discontinued on Day 41. The investigator considered this event to be related to the study medication.

Subject 406 at Site 014, (Protocol 376-404), a 22-year-old Hispanic female with a history of anemia, was randomized to Estrostep. The subject began her normal menses on Day 1. The vaginal bleeding continued instead of ending after a few days as expected. Study medication was discontinued on Day 24, and the vaginal bleeding resolved by Day 30. Concomitant medications included guaifenesin, dextromethorphan, acetaminophen, and dextromethorphan hydrobromide. The investigator considered this event to be related to the study medication.

Subject 420 at Site 014, (Protocol 376-404), a 28-year-old white female with no significant medical history, was randomized to Estrostep. The subject developed breakthrough bleeding on Day 7 and study medication was discontinued on day 12. Concomitant medications included propoxyphene napsylate and doxycycline that was started on Day 14. The investigator considered this event to be related to the study medication.

Subject 470 at Site 017, (Protocol 376-404), a 16-year-old white female with no significant medical history, was randomized to Estrostep. The subject developed vaginal bleeding on Day 96. Study medication was discontinued on Day 101 and the subject recovered by Day 104. Concomitant medications included multivitamin, vitamin E, and St. John's Wort. The investigator considered this event to be related to study medication.

Laboratory Measurements:

Change From Baseline for Clinical Laboratory Measurements

Shifts from baseline to study exit in laboratory parameters are presented in Appendix C.34 and mean changes from baseline to study exit are presented in Appendix C.35.

The only changes in clinical laboratory values with notable differences between treatment

groups occurred in lipid parameters. At study exit, 14 (11%) subjects receiving Estrostep® had changes from normal to high in total cholesterol level compared with 3 (3%) subjects receiving placebo. Mean baseline total cholesterol levels (165 mg/dL) were higher for

Proportion of Subjects With Clinically Significant Laboratory Parameters at Study Exit

At study exit, 49 subjects (Estrostep®,27; placebo; 22) had laboratory parameter values that were possibly clinically significant (Appendices A.7, C.36 and F.4). Of these, 4 parameters had values that were abnormal for greater than 1% of subjects receiving Estrostep. Increases or decreases from baseline of white blood cells to values outside the reference range occurred for 5% of subjects receiving Estrostep® and 2% of subjects receiving placebo. None were considered to be clinically significant.

Elevated triglycerides levels (>200 mg/dL) were found in 5% of Estrostep-treated subjects and in 3% of placebo subjects. Two percent of Estrostep-treated subjects had increases in cholesterol levels to values outside the reference range (>200 mg/dL). Elevations in triglycerides and cholesterol are expected with oral contraceptive use and not of clinical concern at the levels observed.

While 3 (2%) Estrostep-treated subjects had glucose values that were possibly clinically significant, only one subject (001-248) had a value (146 mg/dL) that was of clinical concern at study completion on Day 158. The subject was asymptomatic, and no follow-up information is available.

One additional subject (001-255) receiving Estrostep® had a liver enzyme elevation (SGOT value 69 mU/mL) that was >3 times the upper limit of the reference range at study completion on Day 162. Although the subject was asymptomatic, a repeat blood draw was done 9 days later, and the SGOT value had returned to within the reference range (22 mU/mL).

Other parameters that included <1% of Estrostep® treated subjects were considered not clinically meaningful.

Sponsor did not report any clinically significant changes in blood pressure or weight in either treatment group

XV.-SUMMARY

A.-DEMOGRAPHIC CHARACTERISTICS

Tables S-1 and S-2 summarize the baseline characteristics of the study subjects for both protocols

Table S-1.- Summary . Baseline Demographic Characteristics – Sponsor's Intent-to-Treat Population

Characteristics	376-403 Placebo N =148	Estrostep® N =150	376-404 Placebo N =147	Estrostep® N =146
Age, yr.				
Mean (SD)	23.96 (7.49)	24.99 (7.92)	23.88 (7.38)	23.55 (7.13)
Median (Min, Max)				
Age Category, yr. N (%)				
13-15[a]	22 (15%)	21 (14%)	23 (16%)	17 (12%)
16-17	12 (8%)	13 (9%)	10 (7%)	18 (12%)
18-21	32 (22%)	21 (14%)	30 (20%)	30 (21%)
22-29	45 (30%)	51 (34%)	52 (35%)	59 (40%)
30-39	31 (21%)	39 (26%)	28 (19%)	16 (11%)
40-49	6 (4%)	5 (3%)	4 (3%)	6 (4%)
Race, N (%)				
White/Caucasian	98 (66%)	100 (67%)	104 (71%)	102 (70%)
Black	25 (17%)	18 (12%)	21 (14%)	20 (14%)
Asian	5 (3%)	5 (3%)	2 (1%)	13 (9%)
Hispanic	17 (11%)	20 (13%)	17 (12%)	10 (7%)
Other	3 (2%)	7 (5%)	3 (2%)	1 (1%)
Body Mass Index, kg/m^2				
Mean (SD)	24.85 (5.45)	25.18 (5.53)	25.60 (6.24)	24.42 (6.67)
Median (Min, Max)				

[a] Two subjects less than 14 years of age were protocol exceptions.

Table S-2.-Summary Baseline Clinical Characteristics Sponsor's ITT

Characteristics	376-403 Placebo N =148	Estrostep® N =150	376-404 Placebo N =147	Estrostep® N =146
Total Lesion Count				
Mean (SD)	75.28 (30.35)	77.02 (26.46)	69.22 (24.38)	70.24 (24.95)
Median (Min, Max)				
Inflammatory Lesion Count				
Mean (SD)	29.74 (10.45)	29.28 (10.51)	29.19 (10.06)	29.65 (8.69)
Median (Min, Max)				
Total Comedones				
Mean (SD)	45.55 (25.30)	47.74 (22.85)	40.03 (19.70)	40.59 (21.90)
Median (Min, Max)				

SD =Standard Deviation

Table S-3 shows the number of patients enrolled for the ages 13-15:

Table S-3.- Subjects Age 13-15 participating in Phase 3 studies for acne

	Randomized	Intent-to-Treat	Per-Protocol
13 year old subjects on	2	2	2
13 year old subjects on	0	0	0
14 year old subjects on	17	17	14
14 year old subjects on	23	23	18
15 year old subjects on	19	19	17
15 year old subjects on	22	22	19

Table S-4 points to some demographic differences:

Table S-4.- Demographic differences for both studies

Age	403 placebo	403 active	404 placebo	404 active
18-21	32 (22%)	21 (14%)		
16-17			10 (7%)	18 (12%)
22-29			52 (35%)	59 (40%)
30-39	31 (21%)	39 (26%)	28 (19%)	16 (11%)
Race				
Black	25 (17%)	18 (12%)		
Asian			2 (1%)	13 (9%)
Hispanic			17 (12%)	10 (7%)
Lesion counts				
Total lesion count Median (Min, Max)				
Inflammatory lesion count Median (Min, Max)				
Comedones lesion count Median (Min, Max)				

Subject disposition for both studies is summarized in Table S-5

Table S-5.-Subject Disposition. Comparison for both studies

[Number (%) of Subjects]	376-403		376-404	
Randomized to Treatment	Placebo N = 148	Estrostep® N = 150	Placebo N = 148	Estrostep® N = 147
Early Withdrawal	62 (42%)	48 (32%)	44 (30%)	36 (24%)
Reasons Subjects Withdrew				
Lack of Compliance	4 (3%)	3 (2%)	8 (5%)	4 (3%)
Lack of Efficacy	8 (5%)	3 (2%)	1 (1%)	5 (3%)
Adverse Event	4 (3%)	13 (9%)	3 (2%)	7 (5%)
Pregnancy	5[a] (3%)	0	5 (3%)	1 (1%)
Other/Administrative	41 (28%)	29 (19%)	27 (18%)	19 (13%)
Completed Treatment	86 (58%)	102 (68%)	104 (70%)	111 (76%)

[a] Two additional pregnant subjects (009-326 and 010-494) completed the study. The Pregnancies were unknown until the final visit serum hCG test results were reported.

Differences in subject disposition between the two studies are highlighted in Table S-6

Table S-6.- Highlight of differences in subject disposition for both acne studies

	403 placebo	403 active	404 placebo	404 active
Early withdrawal	62 (42%)	48 (32%)	44 (30%)	36 (24%)
Completed treatment	58%	68%	70%	76%

Reviewer comment: Considering that the number of randomized subjects was the same for both studies, the difference in number of subjects on placebo who completed the study was much greater for 404 than 403, which suggests the studies were somewhat dissimilar. The withdrawals were much higher in study 403 than in 404. Within each study, many more withdrawals for placebo than for active. The withdrawals from 403, placebo, were much higher than for placebo 404

Parke-Davis decided to terminate the studies early by having all subjects complete their close-out visits by January 31, 2000. Decision was made based on the fact that the protocol-specified enrollments had been reached. Expectation was that all subjects in Protocol 376-404 and most subjects in Protocol 376-403 would have had time to complete all their visits by this date. Sponsor considered enrollment was sufficient for the required statistical analysis.

Sponsor used "PT "(planned termination visit) to label a termination visit that occurred before the protocol-scheduled end of study visit (Visit 10). "PT" was assigned for terminations made at the request of the sponsor (e.g., ending the study early or site closure). Sponsor used "ET" to label early terminations for the following reasons: at the subject's or investigator's request or as specifically defined by the protocol (e.g., pregnancy, adverse event).

One hundred sixteen subjects (66 placebo, 50 Estrostep) terminated early from Studies 376-403 and 376-404 due to "other/administrative" reasons. Table S-7 includes all patients who had the designation of PT or ET in their final visit. The most frequent reasons for termination were: "lost to follow-up", "study closed", and "withdrew consent", respectively. The only remaining notable difference between treatment groups regarding a reason for early termination was "busy/scheduling difficulties"; 7 Estrostep- and 0 placebo-treated subjects terminated early for this reason.

Table S-7.-Summary of Sponsor's Reasons[a] for Termination (PT & ET) from Studies 376-403 and 376-404 Due to "Other/ Administrative" Reasons (Number of Subjects)

Reason	Placebo	Estrostep®	TOTAL
Lost to follow-up[b]	24	9	33
Study closed (sponsor terminated study)[c]	17	13	30
Withdrew consent (no other reasons given)[d]	16	11	27
Moved	9	9	18
Busy/Scheduling	0	7	7
Family illness	1	2	3
Perceived lack of efficacy	2	1	3
Dispensing error	1	0	1
Lost study medication	1	0	1
TOTAL	71[e]	52[e]	123[e]

a Sorted by overall, decreasing frequency
b No follow-up information available.
c Includes 27 subjects due to early termination of study and 3 subjects due to closure of study site (see text).
d Includes one placebo-treated subject who was getting married & desired active birth control.
e Seven subjects (3 placebo, 4 Estrostep) gave more than one reason for early termination; therefore, 116 subjects (66 placebo, 50 Estrostep) terminated early.
From Response to additional data request, supplied by sponsor in submission 2000-12-20A

In Study 376-403, 9 placebo- and 8 Estrostep-treated subjects completed at least Visit 7 (Cycle 5) before being withdrawn; the remaining 6 subjects (3 placebo and 3 Estrostep) completed at least Visit 6 (Cycle 4). The average number of days on treatment for subjects who completed at least Visit 7 (Cycle 6) was 138 for placebo-treated subjects and 139 for Estrostep-treated subjects. The average number of days on treatment for subjects who completed at least Visit 6 (Cycle 4) was 115 for placebo-treated subjects and 124 for Estrostep-treated subjects.

There were 3 additional early terminations due to sponsor request. At Site 376-403-14, there was a change in Principal Investigator with a request by the new Investigator to move the study to a different location with a different coordinator. Since only 3 subjects remained on treatment, the study manager decided that it would be less disruptive to the subjects to bring them in early and to close the study at the site. The 3 subjects completed at least Visit 7, Cycle 5.

As a result of this decision by the sponsor, a total of 27 subjects were discontinued early

(designated as PT) from Studies 376-403 (23 subjects) and 376-404 (4 subjects), as shown on Table. S-8.

Table S-8.-Planned Early Terminations (PT): Studies 376-403 & 376-404 and length of treatment achieved

Study Number	Visit	Cycle	Treatment	Site-Subject Number/Initials	Days on Treatment
376-403	7	5	Placebo	9-598	152
				9-595	151
				9-600	141
				9-603	140
				1-243	133
				9-605	132
				4-375	130
				9-607	130
				9-609	130
			Estrostep	9-596	153
				9-599	151
				9-604	141
				9-602	140
				10-50	134
				9-606	133
				9-608	131
				9-610	129
	6	4	Placebo	9-611	128
				17-54	112
				16-54	106
			Estrostep	9-612	125
				9-613	124
				9-614	122
376-404	10	6	Placebo	10-521	168
			Estrostep	10-526	169
	7	5	Placebo	10-528	154
				4-569	140

Concurrent medications:

There were no significant differences in exposure to concurrent medications between the Estrostep® treated group and the placebo-treated group. One subject, 403-009-560, received azathioprine, 50 mg daily, for treatment of colitis. Many subjects took one or more of the following: amoxicillin, azithromycin, bactrim, cephalexin, cefpodoxime, cefuroxime axetil, ciprofloxacin, clarithromycin, [redacted] dirithromycin, doxycycline, erythromycin, fosfomycin, metronidazole, minocycline, nitrofurantoin, oxofloxacin, penicillin, sparfloxacin, sulfamethoxazole, acetaminophen, aspirin, ibuprofen, naproxen, tolmetin, prednisone or one of the antihistamines.

Laboratory tests.

The following table indicates the number of subjects who missed having lab results

Subjects with Missing Lab Panels (Chemistry and Hematology):

	Studies 376-403 and 376-404			
	Baseline		Study Exit	
	403	404	403	404
Missing at least one lab panel	2	5	44	46
Missing both lab panels	0	1[a]	41	43[a]
Missing only chemistry	0	0	0	0
Missing only hematology	2	4	3	3

[a] One subject did not have Baseline or study-exit labs.

Reviewer comment: sponsor supplied a list of 114 subjects with at least one missing lab panel. Two of them failed to have baseline blood drawn for chemistry but had it drawn at study end There were 100 subjects without blood drawn for chemistry at study end

There were 106 subjects who had blood drawn for hematology at baseline but not at study end. There were 6 subjects who had no baseline hematology but did have it at study end

These numbers of subjects without laboratory data make it difficult to assess the rate or significance of laboratory adverse events since some subjects could have eventually had an adverse effect and did not have an opportunity to be detected and be included in the analysis

B.-OVERVIEW OF EFFICACY

Summary of analysis of effectiveness of Estrostep over placebo for both studies [*]

	403								404							
	Per Protocol N= 101 Estrostep® / 86 Placebo				ITT N=150 Estrostep® / 148 Placebo				Per Protocol N= 110 Estrostep® / 102 Placebo				ITT N=146 Estrostep® / 147 Placebo			
Evaluation ▸	Mean of % reduction from baseline		Mean change from baseline		Mean of % reduction from baseline		Mean change from baseline		Mean of % reduction From baseline		Mean change from baseline		Mean of % reduction From baseline		Mean change from baseline	
Lesion Type ▾	%	p	N	P	%	P	N	p	%	p	N	p	%	p	N	p
Inflammatory	5.9	.4409	1.6	.4290	8.3	.0645	2.2	.0515	15.2	.0001	4.7	.0001	12.6	.0022	3.5	.0082
Baseline mean			30/30				29/30				30/29				30/29	
Comedones	13.8	.1937	7.7	.1525	14.5	.0187	6.6	.0197	19.7	.0012	7.5	.0001	15.7	.0038	6.2	.0019
Baseline mean			48/44				41/40				40/42				41/40	
Total	9.3	.1845	9.3	.1501	10.6	.0169	8.7	.0118	17.7	.0001	12.2	.0001	14.5	.0002	9.7	.0004
Baseline mean			78/74				70/69				70/71				70/69	
% Minimal or Better	13.9% (21/ 8%)	.019			9.0% (16/ 7%)	.021			11.9% (22/ 10%)	.009			11.1% (19/ 7%)	.012		

Reviewer comment: A comparison of the results from both studies reveals that the effect for Estrostep® is of small magnitude in both studies. The smallest effect reaching significance is the decrease of inflammatory lesions over placebo for ITT in 404, which was only 3 lesions after 6 months of treatment. One would expect the PP population, which represents subjects who had a more complete treatment, to

obtain a greater effect if the drug product is truly beneficial, but in 403 there were no "wins" for this study population for any lesion counts. In 404, the results for the PP population did reach significance but, again, the magnitude of the effect was very small and simply paralleled those of the ITT population..

Analysis of the Investigator Global Assessment by "absent" alone would provide no wins for either study. The primary efficacy analysis pools together "absent" and "minimal", and the result then reach statistical significance for both 403 and for 404 but the difference between Estrostep® and Placebo is not robust.

These studies are not powered to analyze data in subsets, broken down by age and race. It seems apparent that, at least in this study, the demonstration of efficacy was largely limited to a Caucasian population

Acne Vulgaris Indication Pooled. Data 376-403 and 376-404:
Primary Efficacy Variables Mean Change at Six Months from Baseline [a]

	ESTROSTEP® N=296 (% REDUCTION)	PLACEBO N=295 (% REDUCTION)	TREATMENT DIFFERENCE VS. PLACEBO (95% CI)
Number of inflammatory Lesions			
Mean Baseline	29	29	-3
Mean Reduction from Baseline	15 (52%)	12 (41%)	(-5.0, -1.0)
Number of Comedones			
Mean Baseline	44	43	-6
Mean Reduction from Baseline	17 (38%)	11 (25%)	(-9.5, -2.5)
Number of Total Lesions			
Mean Baseline	74	72	-9
Mean Reduction from Baseline	32 (43%)	23 (32%)	(-13.5, -4.5)

[a] Numbers rounded to nearest integer for Intent to Treat population, as analyzed by the Statistics reviewer

ESTROSTEP was evaluated for the treatment of acne vulgaris in two randomized, double blind, placebo-controlled, multicenter, Phase 3, six-month studies. A total of 295 patients received ESTROSTEP and 296 received placebo. Mean age at enrollment for both groups was 24 years. At six months each study demonstrated a statistically significant difference between ESTROSTEP and placebo for mean change from baseline in lesion counts. The difference in lesion counts from the combined studies was 9 lesions: 6 less comedone lesions and 3 less inflammatory lesions (see Table 3). Each study also demonstrated overall treatment success in the investigator's global evaluation.

C.-QUALITY OF LIFE ASSESSMENT:

Consultation comment by DDMAC (e-mail from Laurie Burke, 4/9/01) conclude that, for regulatory purposes, the meaningfulness in QoL outcomes has not been established. Therefore, this issue is not explored further in this review.

D.-OVERVIEW OF SAFETY

Safety Update

Sponsor prepared a safety update (amendment 006) as had been requested by the Agency on August 16, 2000. Sponsor based the safety update on a review of its database for the period 10/09/96 through 8/31/00, for cases where Estrostep® was a suspect or co-suspect medication. Of these, none of the placebo cases were serious while 17 Estrostep® cases were considered serious, including one case where the patient was reported to have died (Appendix I of Safety Update submission, dated 11/17/01); their narrative is detailed later on in this review.

The Safety update includes:

a) 181 cases of adverse events reported spontaneously to Sponsor by both Health Care Professionals and consumers.
b) 0 cases from adverse event registries and from adverse events published in the medical literature.
c) Cases of serious adverse events reported from clinical studies: 16 cases from Phase 4 clinical studies of Estrostep ® as an oral contraceptive.
d) Cases from the 4 month safety update to the ISS for Estrostep® in the Treatment of Moderate Acne Vulgaris (Phase 3 Clinical Trials 376-403 and 376-404). The ISS contained data on 593 women, of whom 297 received Estrostep® and 296 received placebo for six, 4-week cycles. Of the subjects receiving placebo, 143 (48%) reported adverse events, as did 176 subjects receiving Estrostep® (59%). Of these, there was one Estrostep® case that was considered serious. None of the placebo cases were serious. For the purposes of these studies, unintended pregnancy was captured for tracking purposes, but was not considered an adverse event. While there were 12 pregnancies among the placebo-treated subjects, there was only one pregnancy in the Estrostep@ treated subjects, detailed later in the narrative of the PREGNANCY section

Phase 3 Acne Studies

The age distributions of the cases reported from the acne vulgaris Phase 3 clinical trials is summarized in Table OS-1

Table OS-1.- Number of Cases with Events, by Age for Estrostep® Acne Vulgaris Phase 3 Clinical Trial Cases (All Causality).

Age	Estrostep®	Placebo
(years)	Number of Cases / Number of Subjects (% of Subjects)	Number of Cases / Number of Subjects (% of Subjects)
13-17	37 / 69 (54%)	30 / 67 (45%)
18-49	139 / 228 (61%)	113 /229 (49%)
50+	-	-
Total	176 / 297 (59%)	143 / 296 (48%)

From Table 1a, page 11, item 9, vol 1, dated 11/17/00

The age distributions of the cases spontaneously reported for Estrostep® when used as an oral contraceptive is summarized in Table OS-2

Table OS-2.-Number of Cases with Events, by Age for Estrostep® Spontaneously Reported Cases.

Age (years)	Estrostep® Spontaneously Reported Cases (% of Total Cases)
13-17	1 (< 1%)
18-49	81 (45%)
50+	1 (< 1%)
Unknown	98 (54%)
Total	181

From Table 1b, page 11, item 9, vol 1, dated 11/17/00

Reviewer comment: In over 50% of the post-marketing cases, the age was not reported.

Most Commonly Reported Adverse Events:

Table OS-3.-Events Occurring in >5% of Acne Vulgaris Phase 3 Clinical Trial Subjects, All causality and Adverse Events Attributed to Therapy by Investigator

	Estrostep, (%) of subjects reporting events		Placebo, (%) of subjects reporting events	
Events in Clinical Trials Occurring > 5%	All Causality	Events Attributed to Therapy	All Causality	Events Attributed to Therapy
Metrorrhagia	53 (18%)	51 (17%)	8 (3%)	7 (2%)
Infection	44 (15%)	0	38 (13%)	0
Headache	20 (7%)	11(4%)	28 (9%)	14 (5%)
Flu syndrome	20 (7%)	0	16 (5%)	0
Nausea	19 (6%)	16 (5%)	9 (3%)	6 (2%)
Accidental Injury	15 (5%)	0	9 (3%)	0

From Table 2, page 11, item 9, vol 1, dated 11/17/00

The adverse events reported in three or more cases during what the sponsor calls the post-marketing experience with Estrostep® as an oral contraceptive are summarized in Table OS-4

Table OS-4.- Events Reported in the Post-Marketing database in Three or More Cases (Total Reported Cases = 197)

Adverse Event	Number of cases (% of total)
Unintended Pregnancy	38 (19%)
Lack of Effect	33 (17%)
Menorrhagia	24 (12%)
Off-Label Use	15 (8%)
Emotional Lability	14 (7%)
Pain	13 (7%)
Rash	13 (7%)
Alopecia	11 (6%)
Exposure in Utero	10 (5%)
Nausea	10 (5%)
Depression	8 (4%)
Headache	8 (4%)
Pruritus	7 (4%)
Dyspnea	6 (3%)
Menstrual Disorder	6 (3%)
Weight Gain	6 (3%)

Adverse Event	Number of cases (% of total)
Breast Pain	5 (3%)
Medication Error	5 (3%)
Dizziness	4 (2%)
Libido decreased	4 (2%)
Nausea and vomiting	4 (2%)
Paresthesia	4 (2%)
Amenorrhea	3 (2%)
Anxiety	3 (2%)
Chest Pain	3 (2%)
Deep Thrombophlebitis	3 (2%)
Diarrhea	3 (2%)
Infection	3 (2%)
Leg Cramps	3 (2%)
Nervousness	3 (2%)
Vomiting	3 (2%)

From Table 3, page 12 & 13, item 9, vol 1, dated 11/17/00

A listing of all adverse events reported in at least 3 subjects treated with active and/ or which were more common in the active arm, and those associated with active treatment in subjects randomized during the Phase 3 clinical program is provided in Table OS-5

Table OS-5.-Events Reported During the Estrostep® Acne Vulgaris Phase 3 Clinical Development Program, By Body System, All Randomized Subjects

	All Adverse Events		Associated AE	
Body System/ Adverse Event	Placebo (N=296)	Estrostep (N=297)	Placebo (N=296)	Estrostep (N=297)
BODY AS A WHOLE	88 (30 %)	94 (32 %)	20 (7 %)	18 (6 %)
Abdominal pain	3 (1 %)	12 (4 %)	0 (0 %)	5 (2 %)
Accidental injury	9 (3 %)	15 (5 %)	0 (0 %)	0 (0 %)
Allergic reaction	2 (1 %)	6 (2 %)	0 (0 %)	0 (0 %)
Back pain	4 (1 %)	3 (1 %)	1 (0 %)	0 (0 %)
Congenital anomaly	0 (0 %)	1 (0 %)	0 (0 %)	0 (0 %)
Flu syndrome	16 (5 %)	20 (7 %)	0 (0 %)	0 (0 %)
Headache	28 (9 %)	20 (7 %)	14 (5 %)	11 (4 %)
Infection	38 (13 %)	44 (15 %)	0 (0 %)	0 (0 %)
Malaise	1 (0 %)	1 (0 %)	1 (0 %)	1 (0 %)
Moniliasis	2 (1 %)	3 (1 %)	0 (0 %)	2 (1 %)
Pain	8 (3 %)	7 (2 %)	1 (0 %)	1 (0 %)
Photosensitivity	0 (0 %)	2 (1 %)	0 (0 %)	0 (0 %)
CARDIOVASCULAR	2 (1 %)	12 (4 %)	0 (0 %)	8 (3 %)
Atrial fibrillation	0 (0 %)	1 (0 %)	0 (0 %)	0 (0 %)
Hemorrhage	0 (0 %)	1 (0 %)	0 (0 %)	1 (0 %)
Migraine	2 (1 %)	9 (3 %)	0 (0 %)	7 (2 %)
DIGESTIVE	21 (7 %)	30 (10 %)	10 (3 %)	19 (6 %)
Nausea / vomiting	12(4%)	25 (8 %)	7 (3%)	20 7(%)
Ulcerative stomatitis	0 (0 %)	2 (1 %)	0 (0 %)	0 (0 %)
METABOLIC	5 (2 %)	4 (1 %)	5 (2 %)	2 (1 %)
Hypochromic anemia	0 (0 %)	1 (0 %)	0 (0 %)	0 (0 %)
Increased LDH	0 (0 %)	2 (1 %)	0 (0 %)	0 (0 %)
Weight gain	3 (1 %)	2 (1 %)	3 (1 %)	2 (1 %)
MUSCULOSKELETAL	4 (1 %)	9 (3 %)	1 (0 %)	1 (0 %)
Joint disorder	0 (0 %)	2 (1 %)	0 (0 %)	0 (0 %)
Myalgia	1 (0 %)	3 (1 %)	0 (0 %)	0 (0 %)
Myasthenia	0 (0 %)	1 (0 %)	0 (0 %)	0 (0 %)
NERVOUS	13 (4 %)	18 (6 %)	9 (3 %)	12 (4 %)
Depression	2 (1 %)	3 (1 %)	1 (0 %)	3 (1 %)
Dizziness	3 (1 %)	4 (1 %)	2 (1 %)	3 (1 %)
Emotional lability	4 (1 %)	5 (2 %)	4 (1 %)	4 (1 %)
Grand mal convulsion	0 (0 %)	1 (0 %)	0 (0 %)	0 (0 %)
Hypesthesia	0 (0 %)	1 (0 %)	0 (0 %)	0 (0 %)
Nervousness	4 (1 %)	2 (1 %)	3 (1 %)	2 (1 %)
RESPIRATORY	42 (14 %)	33 (11 %)	0 (0 %)	1 (0 %)
Bronchitis	12 (4 %)	3 (1 %)	0 (0 %)	0 (0 %)
Cough increased	10 (3 %)	5 (2 %)	0 (0 %)	0 (0 %)
Epistaxis	1 (0 %)	2 (1 %)	0 (0 %)	1 (0 %)
Lung disorder	1 (0 %)	3 (1 %)	0 (0 %)	0 (0 %)
Pharyngitis	18 (6 %)	10 (3 %)	0 (0 %)	0 (0 %)
Pneumonia	1 (0 %)	2 (1 %)	0 (0 %)	0 (0 %)
Rhinitis	10 (3 %)	4 (1 %)	0 (0 %)	0 (0 %)
Sinusitis	3 (1 %)	9 (3 %)	0 (0 %)	0 (0 %)
SKIN	14 (5 %)	11 (4 %)	6 (2 %)	5 (2 %)
Alopecia	1 (0 %)	2 (1 %)	1 (0 %)	2 (1 %)
Eczema	0 (0 %)	2 (1 %)	0 (0 %)	1 (0 %)
Herpes simplex	2 (1 %)	3 (1 %)	0 (0 %)	0 (0 %)
Skin discoloration	0 (0 %)	1 (0 %)	0 (0 %)	0 (0 %)
SPECIAL SENSES	6 (2 %)	8 (3 %)	0 (0 %)	3 (1 %)
Conjunctivitis	0 (0 %)	2 (1 %)	0 (0 %)	2 (1 %)
Ear pain	0 (0 %)	1 (0 %)	0 (0 %)	0 (0 %)
Otitis media	2 (1 %)	3 (1 %)	0 (0 %)	0 (0 %)
Taste perversion	0 (0 %)	1 (0 %)	0 (0 %)	1 (0 %)
UROGENITAL	39 (13 %)	78 (26 %)	15 (5 %)	63 (21 %)
Breast engorgement	0 (0 %)	1 (0 %)	0 (0 %)	1 (0 %)
Breast enlargement	0 (0 %)	2 (1 %)	0 (0 %)	2 (1 %)
Breast pain	0 (0 %)	6 (2 %)	0 (0 %)	6 (2 %)
Cystitis	0 (0 %)	1 (0 %)	0 (0 %)	0 (0 %)
Dysmenorrhea	9 (3 %)	10 (3 %)	2 (1 %)	4 (1 %)
Menorrhagia	1 (0 %)	3 (1 %)	1 (0 %)	3 (1 %)
Menstrual disorder	0 (0 %)	4 (1 %)	0 (0 %)	3 (1 %)
Metrorrhagia	8 (3 %)	53 (18 %)	7 (2 %)	51 (17 %)
Unintended pregnancy	9 (3 %)	1 (0 %)	0 (0 %)	0 (0 %)
Urinary frequency	0 (0 %)	1 (0 %)	0 (0 %)	1 (0 %)
Urinary tract infection	3 (1 %)	8 (3 %)	0 (0 %)	0 (0 %)
Uterine disorder	0 (0 %)	1 (0 %)	0 (0 %)	1 (0 %)
Vaginal hemorrhage	0 (0 %)	3 (1 %)	0 (0 %)	3 (1 %)
Vaginal moniliasis	2 (1 %)	3 (1 %)	0 (0 %)	0 (0 %)

From Appendix C.2 of the ISS
Note: Only treatment-emergent adverse experiences are included.

The sponsor summarizes that the adverse events reported were generally consistent for the post-marketing experience with Estrostep® for the acne vulgaris Phase 3 development program, and with the safety profile described in the current labeling for Estrostep®, as well as what has been generally reported for oral contraceptives as a class. Sponsor identified no new safety concerns.

Serious Cases

Other than the unintended pregnancy cases, described under the section Pregnancy, six Phase 4 cases were reported to involve serious adverse events (narratives provided later on in the review), and are summarized in Table OS-6

Table OS-6.-Cases of Serious Adverse Events Reported from Estrostep® Phase 4 Clinical Trials

MCN	Adverse Event(s)	Seriousness Criteria	Causality Assessment	Outcome of Events
001-0376-70152	Pulmonary Embolism	Hospitalization; life threatening	Definitely related	Persisted
001-0376-70153	Blood clots Surrounding Liver; pain in Right side; Back pain	Hospitalization	Possibly related	Recovered
001-0376-980039	Gastritis	Hospitalization	Not related	Recovered
001-0376-980040	Chest pain, Nausea, Faint, Increased Pulse	Medically Significant	Possibly related	Not Reported
001-0376-980049	Enlarging left Ovarian cyst	Hospitalization	Not related	Recovered
001-0376-990031	Hypertension	Life- Threatening	Probably related	Recovered

MCN: Manufacturer's Control Number
From Table 4, page 15, item 9, vol 1, dated 11/17/00

Pulmonary embolism was reported in one of the six cases, in which the causality assessment was that the event was definitely related to the study drug; the patient had not recovered at the time of the report. There were three cases in which the causality assessment was possibly or probably related to study drug, one which reported blood clots surrounding the liver, pain in right side and back pain; another reported chest pain, nausea, faint and increased pulse; and another reported hypertension. The patients recovered in two of these cases and the outcome was unknown in the third. In two cases, the causality assessment was that the events (including gastritis and an enlarging ovarian cyst) were not related or definitely not related to therapy; both patients recovered.

Eleven spontaneously reported cases met the reporting criteria for a serious case. These cases are summarized in Table OS-7

Table OS-7.- Estrostep . Serious Spontaneously Reported Cases.

M.C.N. *	Adverse Event(s)	Seriousness Criteria	Outcome of Events
001-0376-970094	Chest pain, chest pressure, anxiety, bigeminy, PVC's, dry nose, dry mouth, "unable to cope with normal stressors", intermittent shortness of breath	Hospitalization	Dry nose and mouth and shortness of breath persisted; others not reported
001-0376-980025	Uterine bleeding*	Hospitalization	Recovered
001-0376-980034	Gallstones	Hospitalization	Underwent surgery and "did well"
001-0376-980057	Nausea, breakthrough bleeding, overdose*	Overdose	Not reported
001-0376-980096	Pulmonary embolism, deep vein thrombosis, pneumonia, off-label use*	Death	Death
001-0376-980186	Angioedema of the tongue	Hospitalization	Not reported
001-0376-990153	Deep vein thrombosis	Medically significant	Recovered
001-0376-990163	Deep vein thrombosis	Hospitalization	Not reported
001-0376-990191	High antinuclear antibody titer, hair loss	Medically significant	Not reported
001-0376- M0000037	Kidney stone, off-label use	Hospitalization, required Intervention	Persisted
001-0376- M0000111	Blood clots (in vessels behind eyes)*	Medically significant	Not reported

*: **Manufacturer's Control Number.** From Table 5, page 16, item 9, vol 1, dated 11/17/00.
*patient had relevant medical history which may have caused or contributed to the reported adverse events; see case narrative for details

Sponsor reports that vascular and clotting events comprised 4 of the 11 above reported cases, and the one death was related to a clotting event. The patient who died was at high risk, with a history of smoking, an acute pulmonary disorder, and prolonged bed rest. In three cases where the patients were not reported to have died, their medical histories could have contributed to the reported events.

The observation of generally older ages of the women in the post-marketing cases, as compared to the younger ages in the clinical studies (see Table OS-1 and OS-2 above), is most likely related to the specific inclusion of adolescent subjects in the acne vulgaris Phase 3 program. The significance of this and how it might be expected to affect the types of adverse events reported is unknown.

There was one death (001-0376-980096), of a patient with multiple risk factors. The patient was a 30-year-old female, smoker of 1-½ packs of cigarettes daily, who developed pneumonia while on Estrostep®, and was placed on bed rest for approximately two weeks. She experienced leg pain several days before her death. The cause of death was reported as deep vein thrombosis with a pulmonary embolism.

APPEARS THIS WAY
ON ORIGINAL

Narrative Summaries Of Serious Cases:

Acne Clinical Trial Case

Subject 407 at Site 009 in Study 376-403: 17 year old female with a history of exercise induced asthma. On Day 16, she experienced an episode of syncope, followed by head injury from a fall, which resulted in hospitalization. The patient was treated with acetaminophen for subsequent headache. Study medication was continued, and the investigator considered these events as definitely not related to the study medication.

Post-Marketing Cases (N=17)

Case Where the Patient was Reported to Have Died

001-0376-980096: 30-year-old female. History: smoker of 1-½ packs of cigarettes daily in early 1997; exploratory laparoscopy for unknown reason (APR97); possible genitourinary cancer. Concomitant medications: unspecified antibiotic. Started Estrostep® in JAN98 for functional cyst prevention. In FEB98 or MAR98, she developed pneumonia, and was started on an unspecified antibiotic. She experienced a high fever and was placed on bed rest for approximately two weeks. She experienced leg pain several days before her death in MAR98. Estrostep® was apparently discontinued in MAR98. The cause of death was reported as deep vein thrombosis with a pulmonary embolism. A physician reported this case.

All Other Post-Marketing Cases, listed by Manufacturer Control Number

Phase 4 Clinical Trial Cases

001-0376-970152: 29 year old white female in "post marketing" (376-400, #287606). History: unknown. Concomitant medications: unknown. Started Estrostep® on 11AUG97. She was hospitalized on 29OCT97 for pulmonary embolism, treated with heparin. Estrostep® therapy was discontinued on 29OCT97. She had not yet recovered as of the date of the report (03NOV97). This case was reported by a health care professional.

001-0376-970153: 42 year old female in "post marketing" (376-400, #162008). History: unknown. Concomitant medications: unknown. Started Estrostep® on 21SEP97. She was seen in an emergency room on 12OCT97 for right side and back pain and dismissed after unknown tests were inconclusive. Estrostep® therapy was discontinued on 12OCT97. She was hospitalized on 23OCT97 for pain, and found to have blood clots surrounding the liver, and was treated with [redacted] She was discharged "feeling 100% better." A physician reported this case.

001-0376-980039: 20 year old white female in "post marketing" (376-400, #130604). History: unknown. Concomitant medications: none. Started Estrostep® on 20OCT97. She experienced gastritis on 22NOV97 and was hospitalized on the same day to rule out appendicitis. Estrostep® therapy was discontinued on 22NOV97, and resumed following her next period, on an unknown date. She recovered from the gastritis. A physician reported this case.

001-0376-980040: 21 year old female in "post marketing" (376-400, #160903).

History: none. Concomitant medications: unknown. Started Estrostep® on 12OCT97. She experienced chest pain, faint, nausea, increased pulse, dizziness, and short of breath, and was seen in an emergency room on 07NOV97. An erratic EKG was found. A cardiologist, who advised discontinuation of Estrostep, saw her; therapy was discontinued on 07NOV97. Recovery status is unknown as of the date of the latest report (06FEB98). A physician and a nurse reported this case.

001-0376-980049: 19 year old white female in "post marketing" (376-400, #unspecified). History: adnexal complex mass diagnosed 20OCT97. Concomitant medications: pseudoephedrine/ loratadine. Started Estrostep® on 09NOV97. She was diagnosed as having an enlarging complex left ovarian cyst, which led to hospitalization and an operative laparoscopy on 16DEC97. Estrostep® therapy was discontinued on 16DEC97. She recovered uneventfully. Oral contraceptive pills were not resumed as of the date of the latest reports (09MAR98). A nurse reported this case.

001-0376-990031: 31 year old white female in "post marketing" (376-400-400, #340210). History: unknown. Concomitant medications: none. Started Estrostep® on 16NOV97. She experienced hypertension, with a blood pressure (BP) reading of 168/104 in JAN98, which was considered life threatening by the investigator, and drug was discontinued on 05JAN98. BP on 02JUN98 was 164/84. The patient was considered to have recovered. A physician reported this case.

Spontaneously Reported Cases

001-0376-970094: Unknown age female with history of endometriosis. Concomitant medications: unknown. Several weeks after starting Estrostep® on 6APR97 for treatment of endometriosis, she experienced dry nose and mouth, and intermittent shortness of breath 2-3 times daily. On 13JUN97, she experienced chest pain and pressure, and was hospitalized with bigeminy and premature ventricular contractions. Studies for myocardial infarction were negative. Estrostep® therapy was continued. This case was reported by the patient.

001-0376-980025: 20-year-old female. History: Surgical abortion for fetal anomalies 2 weeks before beginning drug. Concomitant medications: none. Started Estrostep® on 13NOV97. She was hospitalized on 28DEC97 for uterine bleeding of two days' duration. Estrostep® therapy was discontinued on 28DEC97. She recovered on 30DEC97. This case was reported by a physician, who thought that the bleeding was a return to menses.

001-0376-980034: Unknown age female. History: none reported. Concomitant medications: none. Started Estrostep® on unknown date. She developed gallstones on an unknown date, and was hospitalized on 03MAR98 for a cholecystectomy. Estrostep® therapy status is unknown. The physician reported that the patient "did well." This case was reported by a physician.

001-0376-980057: Unknown age female. History: unknown. Concomitant medications: unknown. Started Estrostep® on unknown date. After forgetting to take Estrostep® on two consecutive days and on the third day, taking three tablets, she experienced breakthrough bleeding, nausea, and was "queasy". Recovery status is unknown as of the date of the report (17MAR98). This case was reported by the patient.

001-0376-980186: Unknown age female. History: unknown. Concomitant medications: unknown. Started Estrostep® on 08DEC98. She developed angioedema of the tongue on 08DEC98, after the first dose of Estrostep®, leading to hospitalization on 10DEC98. Estrostep® therapy was discontinued on 10DEC99. Recovery status is unknown as of the date of the latest report (25JAN99). This case was reported by a pharmacist.

001-0376-990153: 28-year-old female. History: no smoking nor drinking. Concomitant medications: none. Started Estrostep® in JUL99. She developed deep vein thrombosis, and was treated with Coumadin and has recovered. Estrostep® was discontinued in SEP99. This case was reported by a health professional.

001-0376-990163: 35-year-old female. History: none reported. Concomitant medications: none reported. Started Estrostep® on unknown date. She developed deep vein thrombosis, leading to hospitalization. Estrostep® therapy status and recovery status were unknown as of the date of the report (20OCT99). This case was reported by a health professional.

001-0376-990191: 28-year-old female. History: strong psychological concern for her upcoming wedding. Concomitant medications: isotretinoin from 25AUG99 to 22OCT99. Ongoing Estrostep® therapy was initiated on 01AUG99. The patient experienced an elevated antinuclear antibody titer (1:640) which was considered medically significant (test date not reported) and minimal hair loss that was regarded as normal. The outcome was unknown. The case was reported by a physician.

001-0376-M0000037: 19-year-old female. History: no history of kidney stones. Concomitant medications: none. Started Estrostep® in 1997. Starting in JUL99, she developed approximately 12 kidney stones, leading to several hospitalizations and surgical interventions. Some stones passed spontaneously. A 24-hour urine test for calcium was normal. Estrostep® therapy continues. She has a persistent stone as of the date of the latest report (09MAR00). This case was reported by the consumer.

001-0376-M0000111: Unknown age female. History: diabetes. Concomitant medications: unknown. Started Estrostep® in MAR98. She developed blood clots in the vessels behind her eyes. She was seen by two ophthalmologists. One thought that her birth control pill was probably responsible, and the second thought that her diabetes was probably the etiology for her problem. Estrostep® was discontinued in APR00.Recovery status is unknown at the time of the latest report (10MAY00). This case was reported by a physician.

Pregnancy

A total of 40 cases of pregnancy involving patients taking Estrostep® during the Post-marketing experience were identified.

Of these, 38 cases reported events that were encoded as "unintended pregnancy", and two additional cases were reported to involve drug exposure to Estrostep® during pregnancy (which encode to "medication error"). These included 10 cases reported from "post marketing" and 30 spontaneous reports (four from consumers and 26 from health professionals). One spontaneous report (#001-0376-980022), submitted by an "unknown" physician via a company representative, stated that an "unspecified number" of patients became pregnant while taking Estrostep®; no additional information was provided.

During the acne vulgaris Phase 3 clinical program there was one case of unintended pregnancy among 297 women (0.3%) treated with Estrostep® and 12 cases of unintended pregnancy among 296 women (4%) receiving placebo. Among the 10 clinical study cases, seven reported that conception occurred after Estrostep® was discontinued. Five of the seven cases reported the date of last pre-pregnancy menstruation to have occurred after the therapy cessation date. The estimated date of conception (reported in all seven cases) ranged from 1.5 to 5.5 weeks after therapy was discontinued. Three cases were reported to have involved non-compliance. Six cases specifically reported that the patient was compliant in taking Estrostep®; however, in one of these cases (#001-0376-990047) it was reported that the patient had vomited on four consecutive days after taking Estrostep®. In another case (#001-0376-M0000135), it was specifically reported that the date of conception "proceeded" the expiration date of the Estrostep® lot that she had been dispensed. None of the cases documented administration of concomitant medications that have been reported to decrease the efficacy or plasma levels of oral contraceptives, such as anticonvulsants, troglitazone, phenylbutazone, rifampin or antibiotics. The outcome of the pregnancy was reported in nine cases. One spontaneous case (#001-0376-990133) reported the birth of a healthy infant. Eight patients, including three from clinical study cases, elected to abort the pregnancy. The outcome was unknown in the remaining 31 cases; however, five of these 31 cases reported an estimated delivery date, implying that the mother intended to continue the pregnancy to term.

As is the case for other oral contraceptive products, Estrostep® is labeled with pregnancy category X (contraindicated for use during known or suspected pregnancy). Sponsor comments that epidemiologic studies have not suggested that inadvertent use of oral contraceptives during early pregnancy involve an increased risk of teratogenic effects, particularly for cardiac anomalies and limb reduction defects.

Next is the narrative of one pregnancy that occurred, in an Estrostep® treated subject (while conducting the studies included in this NDA.)

Subject 376-404-007-343, a 27-year-old white female with no significant medical history, was randomized to Estrostep. Concomitant medications included ibuprofen, caffeine, and phenylpropanolamine. She had a negative serum pregnancy test 36 days before randomization and a negative urine pregnancy test at randomization (the date of her first dose of Estrostep). She also reported that the first day of her last menstrual period was 5 days before randomization and

that it was a normal period. After taking study medication (1 mg NA/20 μg EE) for 3 days, the subject reported having a positive urine pregnancy test; results of a serum (hCG) pregnancy test taken that same day were also positive. At that time, she discontinued study medication and was withdrawn from the study. On January 1, 2000 (Study Day 256: 253 days post treatment), she delivered a healthy, 8 LB, 2 oz girl by cesarean section, with no noted congenital anomalies or defects. This was her first child.

The scheduled 6-month follow-up contact was not made until the baby was 9 months old (September 20, 2000) due to an inability to contact the mother. At this time, it was reported that although the baby was healthy, magnetic resonance imagery had detected spina bifida occulta; this was repaired surgically on June 9, 2000, when the baby was 6 months old (WAERS/Mfr. Report 001-0376-M0000298). This anomaly was not noted at birth and was considered by the investigator as unlikely to be related to study drug. The baby's medical records were requested by the investigator but the parents have decided not to release them.

OPDRA report of adverse events

Other serious adverse event is deep vein thrombosis and pulmonary embolism (PE). A review by OPDRA, dated 2/20/01, has revealed 149 cases of pulmonary embolism with OCP containing the same ingredients found in Estrostep®, 36 of which ended in death of the patient. Two cases of PE have been reported for Estrostep®. Other adverse events reported for Estrostep® include:

2 pulmonary embolism (PE)
2 Deep Vein Thrombosis (DVT)
1 blood clot
3 breakthrough bleeding
2 headaches
2 Hypertension (HTN)
2 rash
2 unintended pregnancy
1 loss of libido
1 and alopecia
1 allergic reactions
1 angioedema
1 hot flashes
1 gallstones
1 kidney stones
1 myalgia

XVI.-CONSIDERATIONS ON RISK BENEFIT

A.-COMPARISON OF INTERMENSTRUAL BLEEDING:

The original review of NDA 20-130, Estrostep® for the indication oral contraception compared the rate of intermenstrual bleeding for several oral contraceptives as shown in the following table :

Comparison of rate of Intermenstrual bleeding for several oral contraceptives From MOR NDA Review OF NDA 20-130 Estrostep® Dated 8/31/91 Pg. 4

Tri-Norinyl	10-25% IMB	End of 4th cycle	
Ortho-Novum 7/7/7	<10%	At cycle 4	
Modicon	About 20%	Cycle 4	
Ortho-Novum 10/11	10%	Cycle 4	
Ortho-Novum 1/35	10%	Cycle 4	
Ortho-Novum 1/50	10%		
Triphasil	10.5%		
Loestrin 1/20	44%		This was a poorly controlled study with a different formulation of Estrostep
Loestrin 1.5/30	23%		
Loestrin 1/50	23%		
Estrostep®1/20, 1.5/30, 1/50	23%		

From this table, one could expect a greater rate of intermenstrual bleeding from Estrostep® than from other similar oral contraceptives.

The original review for Estrostep® for the indication oral contraception also collected information about the rate of breakthrough bleeding/spotting for this drug product as compared to similar oral contraceptives, as shown in the following table:

Comparison of breakthrough bleeding/spotting for several oral contraceptives. From MOR NDA Review OF NDA 20-130 Estrostep® Dated 8/31/91 Pg. 11

	Estrostep	Loestrin	P value	Acne protocol as reported by sponsor
Cycle 1	58%	46	.001	
Cycle 2	39%	27	.001	
Cycle 3	22	17	.037	
Cycle 4	22	16	.010	
Cycle 5	17	10	.001	
Cycle 6	17	13	.087	
Overall	76%	64%	.001	17% average (14 -27% each study)
Average/cycle	33%	25	.001	
Mean duration	1.89 days	1.58	.010	
Time to first episode (mean)	16	41	.001	

The difference in bleeding episodes between Estrostep® and Loestrin was a statistically significant difference for the first 5 cycles and over the total of 6 cycles. It was unclear if it was a clinically significant difference.

It is interesting to underline the great difference between the rate of bleeding as reported in the original NDA for contraception and the sponsor's reported 17% rate for metrorrhagia in the

combined population of both acne studies was (14% for one and 27% for the other). This adverse event was severe enough to require discontinuation of treatment in at least 3 Estrostep® treated subjects

B.-COMPARISON OF OTHER ADVERSE EVENTS (OVARIAN CYSTS):

The original review for Estrostep® for the indication oral contraception also collected information about the rate of ovarian cyst development for this drug product as compared to Loestrin, a similar oral contraceptives, as shown in the following table:

Development of ovarian cysts based on her initial review of 3 cycle vaginal ultrasound subgroup study. From MOR NDA Review OF NDA 20-130 Estrostep® Dated 8/31/91 Pg. 21

Estrostep	18% over 3 treatment cycles (n=15 in 769 patients)	2 in acne study 447 patients (0.45%)
Loestrin	8% (n=13 in 508 patients)	

The Medical Reviewer noted that no statistical analysis was made but thought these differences appeared highly significant

In the acne studies no ultrasound studies were routinely conducted. The incidence of ovarian cyst formation may have been unreported.

C.-COMPARISON OF CONTRACEPTIVE EFFICACY:

The original review for Estrostep® for the indication oral contraception also compared the rate of pregnancy development for this drug product to that of similar oral contraceptives. For this purpose, the PEARL INDEX is used, as shown in the following table :

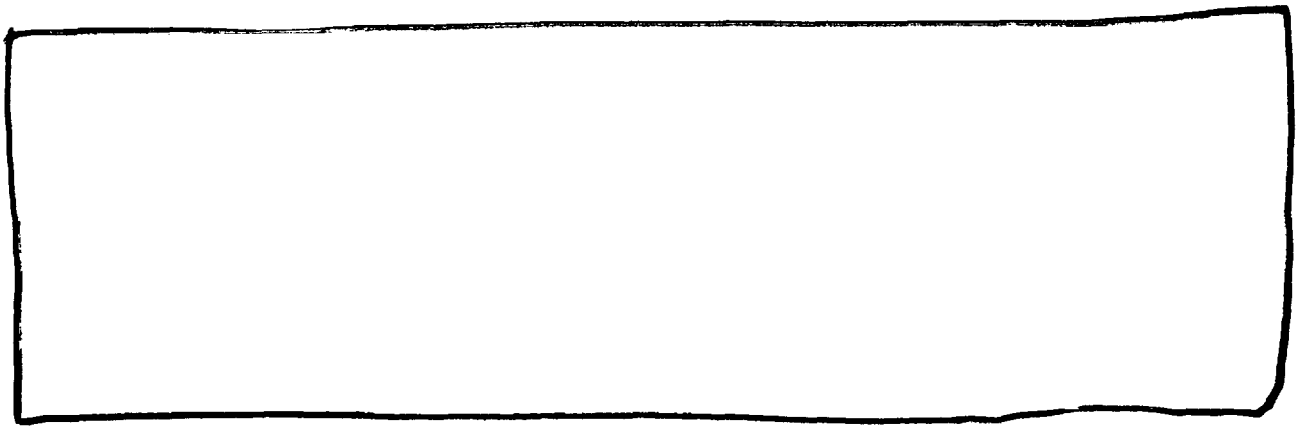
Comparison of PEARL INDEX for several oral contraceptives. From MOR NDA Review OF NDA 20-130 Estrostep® Dated 8/31/91 page 14

OCP	Pearl Index		Estrostep® Acne study
Loestrin 1/20[1]	0.75		
Loestrin 1.5/30[3]	0.49		
Norlestrin 1/50[3]	0.05		
Norlestrin 2.5/50[3]	0.22		
Triphasil	0.33		
Estrostep	2.4[1]	26 in 769 patients	1 case only for 297 patients[2]

[1] As recalculated by MO NDA Review after including all reported pregnancies

[2] It is unclear why the number of reported pregnancies in the acne study were much lower than in the original NDA submission. It is possible that the confidence interval for the expected number of pregnant subjects in the Estrostep® acne study based upon the original NDA pearl index could include 1.

Using the following formula for the pearl index, as per MOR NDA review of NDA 20-130,



D.-POTENTIAL FOR PREMATURE EPIPHYSEAL CLOSURE IN POSTMENARCHEAL ADOLESCENTS TAKING ORAL CONTRACEPTIVES

Following written consultation with the Divisions of Metabolic and Endocrine Drug Products (10/27/00) and of Reproductive and Urologic Drug Products (1/22/01), it was felt that:

- In general, premature epiphyseal closure should not be a concern for females who are one year post menarche although there may be a small to modest effect on final height if treatment is started at one-year post-menarche. The possibility that use of Estrostep prior to this point may reduce final height should obviously be weighed against the need for contraception (and treatment for acne). To minimize the potential for reduction in final height, the bone age, as determined by bone density, should be at least 15 years.
- Ethinyl estradiol has been used , in doses as low as 0.02 to 0.05 mg/day (as in Estrostep) to decrease the final height of adolescents with 'constitutional tall stature'
- It has been reported that the younger a girl was at onset of estrogen treatment, the more her adult height could be reduced
- It has been reported that adolescent females during the first year after menarche had an incidence of 61.5% open epiphyses
- In women of any age, signs of hyperandrogenism, such as severe acne, should be further evaluated for possible pathology (e.g. adrenal hypertrophy)
- Safety and efficacy of oral contraceptives is expected to be similar for subjects 16 years old and above

LITERATURE QUOTATIONS:

This reviewer is including some quotations from several publications, thought to be relevant for the recommendations made in this review:

A.-From the October 2000 SUPPLEMENT TO OBG. MANAGEMENT:

a.1.- "50% of teenagers are reported to discontinue use of OCT within 3 months"

a.2.- expected rate of adverse events:

Expected rate of adverse event for various oral contraceptives

	Oral contraceptive				
	Estrostep	Ortho-Tricyclen	Alesse	TriNorinyl	LoOvral
Bleeding in 3rd cycle	26.2%	17.7%	26.5	25%	9.6
Estrogenic activity[a]	16	35	17	40	25
Progestetional[b]	1.2	0.3	0.5	0.7	0.8
Androgenic[c]	0.53	0.15	0.31	0.23	0.46

[a]: comparative potency based on oral rat vaginal epithelium assay Jones RC *Fertil Steril 1973: 24-284-291*

[b]: based on amount required to induce vacuoles in human endometrium: Phillips A. *Contraception: 1990, 41:399-410*

[c]: comparative potency based on rat ventral prostate assay. Phillips A. *Contraception: 1990, 41:399-410*

B.-From : Balassone ML Journal Adolescent Health Care 1989: 10: 527-533

This study prospectively assessed the use of OCP in adolescents and reported that about half of the study population never returned to a follow up visit. On telephone follow up, all had discontinued the OCP. This lack of continuity of treatment with oral contraceptives has been reported in many other studies. Of those who took them, many were inconsistent, forgetting to take the pill around 3.4 times a month on average, impacting on efficacy

Reviewer comments on Risk-benefit :

The concern remains that oral contraceptives could potentially result in epiphyseal closure and reduced height in females who use oral contraceptives soon after menarche although there is no clear scientific data to show that it does

Many teenagers are likely to remain on the OCP for less time than is needed to see improvement in acne as the result of OCP treatment. This point is corroborated by the rate of completed treatment which was 68% for the Estrostep® acne study. Outside of a controlled clinical study, such as in every day practice of medicine, one would expect the dropout rate to be even higher

Therefore, a great number of patients would be exposed to hormones and would either withdraw from treatment within the first 3 months, before benefit can be observed -

specially if they are young- or would continue treatment and observe no improvement or, in best of cases, scant improvement, barely better than if they had placebo. By the time they withdraw, they will have experienced most of the expected adverse events and none of the benefits.

The sponsor claims oral contraceptives are less risky than pregnancy. However, it is clear that oral contraceptives are far riskier than acne and quite likely riskier than most other internal treatments available for acne.

For study 403, there is a "win", in the Intent-to-Treat population, only for comedones and total lesions, not for inflammatory lesions. The Estrostep treatment effect over placebo, at the end of the study (6 months), is only 6 for comedones and 8 for total lesions and the per-protocol population is not supportive of that "win"

For study 404, where sponsor claims a "win" for the three lesion counts, the Estrostep treatment effect over placebo is 3 for inflammatory lesions, 6 for comedones, and 9 for total counts. The per-protocol-population is supportive but the Estrostep treatment effect is similarly small: 4 for inflammatory lesions, 7 for comedones, 12 for total lesion counts, after 6 months of treatment. This degree of decrease in lesion counts of active over placebo would not outweigh the risks of hormonal treatment.

Acne patients who do not desire contraception are likely to obtain significant improvement from other oral anti-acne medications after only 3 or 4 weeks of treatment, and be practically cleared of acne in 4-6 months. Patients with acne who desire contraception ought to consider whether to choose oral contraceptives or some different contraception method. Since there is a theoretical concern that oral anti-acne treatments may interfere with the contraceptive effect of oral contraceptives, if they choose an oral contraceptive, they will deprive themselves of the earlier and greater benefits one could expect from other oral anti-acne treatments. That would not be the case if they choose a different type of contraception

Additionally, from earlier reviews of the drug product:

- *it seems Estrostep® is not the best or the safest oral contraceptive*
- *it has a greater array of adverse events than other contraceptives*

XVII.- SUMMARY AND EVALUATION:

ESTROSTEP was evaluated for the treatment of acne vulgaris in two randomized, double blind, placebo-controlled, multicenter, Phase 3, six-month studies. A total of 295 patients received ESTROSTEP and 296 received placebo. Mean age at enrollment for both groups was 24 years. At six months each study demonstrated a statistically significant difference between ESTROSTEP and placebo for mean change from baseline in lesion counts. The difference in lesion counts from the combined studies was 9 lesions: 6 less comedone lesions and 3 less inflammatory lesions (see Table 3). Each study also demonstrated overall treatment success in the investigator's global evaluation.

The sponsor has supplied efficacy and safety studies in support of use of the drug product Estrostep® for the indication acne. The studies show some effect, statistically significant in both studies. The amount of benefit observed was not clinically robust and was observed only after at least 6 months of treatment. The number of subjects under the age of 15 was too small to suggest reducing the age of treatment below the age of 15, where there is a greater possibility of epiphyseal closure. Few medical practitioners would undertake a bone density study of adolescent females prior to commencing oral contraceptive treatment of acne.

XVIII. PEDIATRIC WAIVER.

SPONSOR'S REQUEST FOR PARTIAL PEDIATRIC WAIVER FOR COLLECTION OF SAFETY, EFFICACY, AND FOR PHARMACOKINETIC DATA OF ESTROSTEP® IN FEMALES <14 YEARS OF AGE

Sponsor is requesting a partial waiver from the study of Estrostep in females <14 years of age for the treatment of moderate acne vulgaris because; (1) moderate acne vulgaris is uncommon in females <14, and (2) oral contraceptives are not indicated for women prior to menses due to theoretic concerns over the premature advancement of bone age and its impact on final adult height. OCPs have generally been studied in women 18 and older and some studies have included girls as young as 15. In practice, OCPs are considered safe for girls younger than 16, as long as they are already menstruating.

The mean age of menarche is 12.16 ± 2 years. The concern about treating younger girls with OCPs is based on the theoretic possibility of advancing their bone age prematurely prior to completion of their pubertal "growth spurt." The adolescent "growth spurt" in girls begins at a mean age of 9.6 years. At a mean age of 12.2 years, a girl begins menses, and she will have attained nearly 97% of her final adult height. Following menses, there is a slow, gradual increase in height until final adult height is achieved by approximately age 18.

Sponsor set the age cut-off for the acne studies at 14. There were few subjects exposed to Estrostep® younger than 18, an age where pharmacokinetics of ethinyl estradiol and norethindrone had not been previously determined. Sponsor conducted such studies in a few subjects within that age group and plans no other studies at this time. Estrostep is unlikely to offer a therapeutic benefit to females <[redacted] years of age in treatment of acne and its use in this pediatric age group could pose theoretic risks regarding bone growth. Therefore, we request a waiver for collection of safety, efficacy and pharmacokinetic data in females <[redacted] years of age.

> *Reviewer comment: since the drug would be approved only for use in females 15 or older, who have started to menstruate, want contraception with an oral contraceptive, can tolerate such oral contraceptive, plan to be on it for at least 6 months, and have moderate acne which has not responded to topical anti-acne medications, this reviewers considers a partial waver can be granted to the sponsor from having to Collect Safety, Efficacy, and Pharmacokinetic Data of Estrostep® in Females <15 Years of Age.*

XVII.- MEDICAL REVIEW OF LABEL :

ESTROSTEP[01]®
(Norethindrone Acetate and Ethinyl Estradiol Tablets, USP)

ESTROSTEP® 21

(Each white triangular tablet contains 1 mg norethindrone acetate and 20 mcg ethinyl estradiol; each white square tablet contains 1 mg norethindrone acetate and 30 mcg ethinyl estradiol; each white round tablet contains 1 mg norethindrone acetate and 35 mcg ethinyl estradiol.)

ESTROSTEP® Fe

(Each white triangular tablet contains 1 mg norethindrone acetate and 20 mcg ethinyl estradiol; each white square tablet contains 1 mg norethindrone acetate and 30 mcg ethinyl estradiol; each white round tablet contains 1 mg norethindrone acetate and 35 mcg ethinyl estradiol; each brown tablet contains 75 mg ferrous fumarate.)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

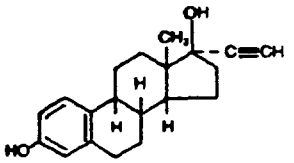
Estrostep is a graduated estrophasic providing estrogen in a graduated sequence over a 21-day period with a constant dose of progestogen.

Estrostep 21 provides for a 21-day dosage regimen of oral contraceptive tablets.

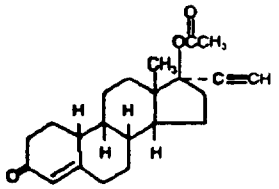
Estrostep Fe provides for a continuous dosage regimen consisting of 21 oral contraceptive tablets and seven ferrous fumarate tablets. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen, are non-hormonal, and do not serve any therapeutic purpose.

Each white triangle-shaped tablet contains 1 mg norethindrone acetate [(17 alpha)-17-(acetyloxy)-19-norpregna-4-en-20-yn-3-one] and 20 mcg ethinyl estradiol [(17 alpha)-19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol]; each white square-shaped tablet contains 1 mg norethindrone acetate and 30 mcg ethinyl estradiol; and each white round tablet contains 1 mg norethindrone acetate, 35 mcg ethinyl estradiol. Each tablet also contains calcium stearate; lactose; microcrystalline cellulose; and starch.

The structural formulas are as follows:



Ethinyl Estradiol



Norethindrone Acetate

Each brown tablet contains microcrystalline cellulose; ferrous fumarate; magnesium stearate; povidone; sodium starch glycolate; sucrose with modified dextrins.

Each Estrostep 21 tablet dispenser contains five white triangular tablets, seven white square tablets, and nine white round tablets. These tablets are to be taken in the following order: one triangular tablet each day for five days, followed by one square tablet each day for seven days, and then one round tablet each day for nine days.

Each Estrostep Fe tablet dispenser contains five white triangular tablets, seven white square tablets, nine white round tablets, and seven brown tablets. These tablets are to be taken in the following order: one triangular tablet each day for five days, then one square tablet each day for seven days, followed by one round tablet each day for nine days, and then one brown tablet each day for seven days.

CLINICAL PHARMACOLOGY

ORAL CONTRACEPTION

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

In vitro and animal studies have shown that norethindrone combines high progestational activity with low intrinsic androgenicity. In humans, norethindrone acetate in combination with ethinyl estradiol does not counteract estrogen-induced increases in sex hormone binding globulin (SHBG). Following multiple-dose administration of Estrostep, serum SHBG concentrations increase two- to three-fold and free testosterone concentrations decrease by 47% to 64%, indicating minimal androgenic activity.

ACNE

Acne is a skin condition with a multifactorial etiology. [redacted]

and norethindrone acetate [redacted] increase sex hormone binding globulin (SHBG) and decrease free testosterone [redacted] a decrease in the severity of facial acne in otherwise healthy women with this skin condition.

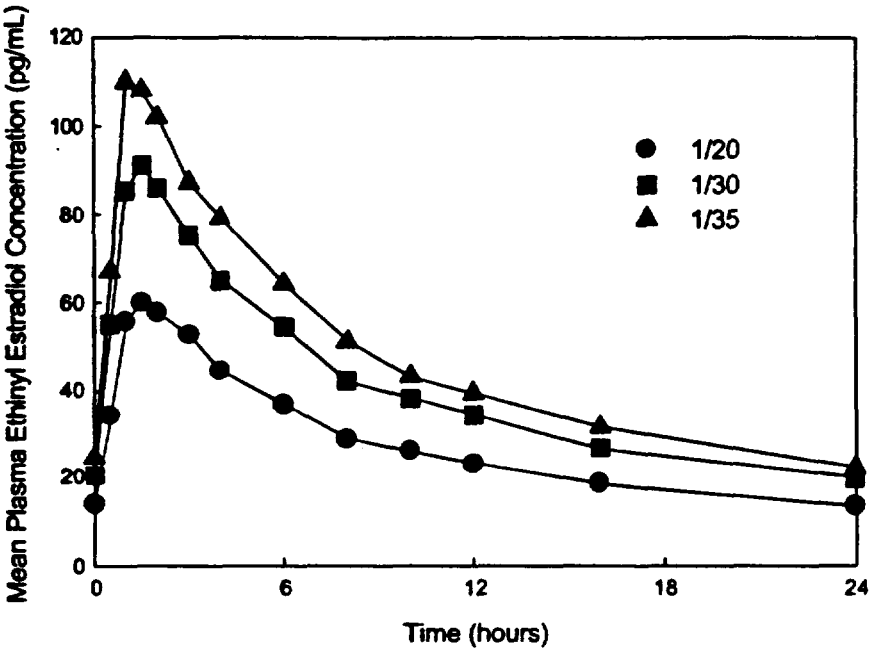
Pharmacokinetics

Absorption

Norethindrone acetate appears to be completely and rapidly deacetylated to norethindrone after oral administration, since the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone [redacted] Norethindrone acetate and ethinyl estradiol are rapidly absorbed, with maximum plasma concentrations of norethindrone and ethinyl estradiol occurring 1 to 2 hours postdose. Both are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 43% for ethinyl estradiol (1-3).

Administration of norethindrone acetate/ethinyl estradiol with a high fat meal decreases rate, but not extent, of ethinyl estradiol absorption. The extent of norethindrone absorption is increased by 27% following administration with food.

Plasma concentrations of norethindrone and ethinyl estradiol following chronic administration of Estrostep to 17 women are shown below (Figure 1). Mean steady-state concentrations of norethindrone for the 1/20, 1/30, and 1/35 tablet strengths increased as ethinyl estradiol dose increased over the 21-day dose regimen, due to dose-dependent effects of ethinyl estradiol on serum SHBG concentrations (Table 1). Mean steady-state plasma concentrations of ethinyl estradiol for the 1/20, 1/30, and 1/35 tablet strengths were proportional to ethinyl estradiol dose (Table 1).



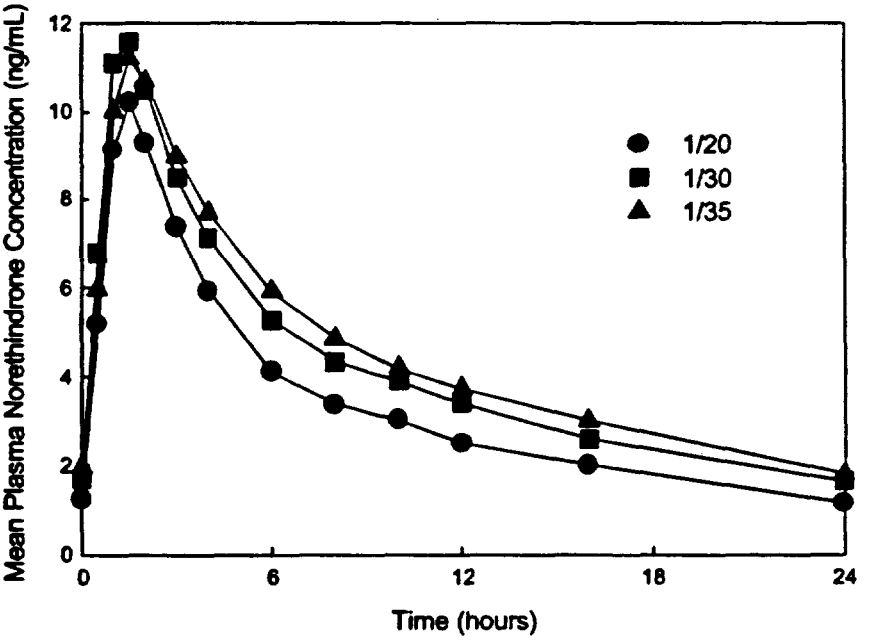


Figure 1. Mean Steady-State Plasma Ethinyl Estradiol and Norethindrone Concentrations Following Chronic Administration of Estrostep

Table 1. Mean (SD) Steady-State Pharmacokinetic Parameters [a] Following Chronic Administration of Estrostep

Norethindrone Acetate/Ethinyl Estradiol Dose	Cycle Day	Cmax	AUC	CL/F	SHBG [b]
		Norethindrone			
mg/μg		ng/mL	ng·hr/mL	mL/min	nmol/L
1/20	5	10.8	81.1	220	120
		(3.9)	(28.5)	(137)	(33)
1/30	12	12.7	102	166	139
		(4.1)	(32)	(85)	(42)
1/35	21	12.7	109	152	163
		(4.1)	(32)	(73)	(40)
		Ethinyl Estradiol			
mg/μg		pg/mL	pg·hr/mL	mL/min	nmol/L
1/20	5	61.0	661	549	
		(16.8)	(190)	(171)	
1/30	12	92.4	973	546	
		(26.9)	(293)	(199)	
1/35	21	113	1149	568	
		(44)	(372)	(219)	

[a] Cmax = Maximum plasma concentration; AUC(0-24) = Area under the plasma concentration-time curve over the dosing interval; CL/F = Apparent oral clearance

[b] Mean (SD) baseline value = 55 (29) nmol/L

Distribution

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg (1-3). Plasma protein binding of both steroids is extensive (>95%); norethindrone binds to both albumin and sex hormone binding globulin, whereas ethinyl estradiol binds only to albumin (4). Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis. Estrostep increases serum SHBG concentrations two- to three-fold (Table 1).

Metabolism

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites (5). A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol. Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation

Excretion

Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites [redacted] Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg) [redacted] Steady-state elimination half-lives of norethindrone and ethinyl estradiol following administration of Estrostep are approximately 13 hours and 19 hours, respectively.

Special Population

Race

The effect of race on the disposition of Estrostep has not been evaluated.

Renal Insufficiency

The effect of renal disease on the disposition of Estrostep has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged compared to concentrations in premenopausal women with normal renal function.

Hepatic Insufficiency

The effect of hepatic disease on the disposition of Estrostep has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function.

Drug-Drug Interactions

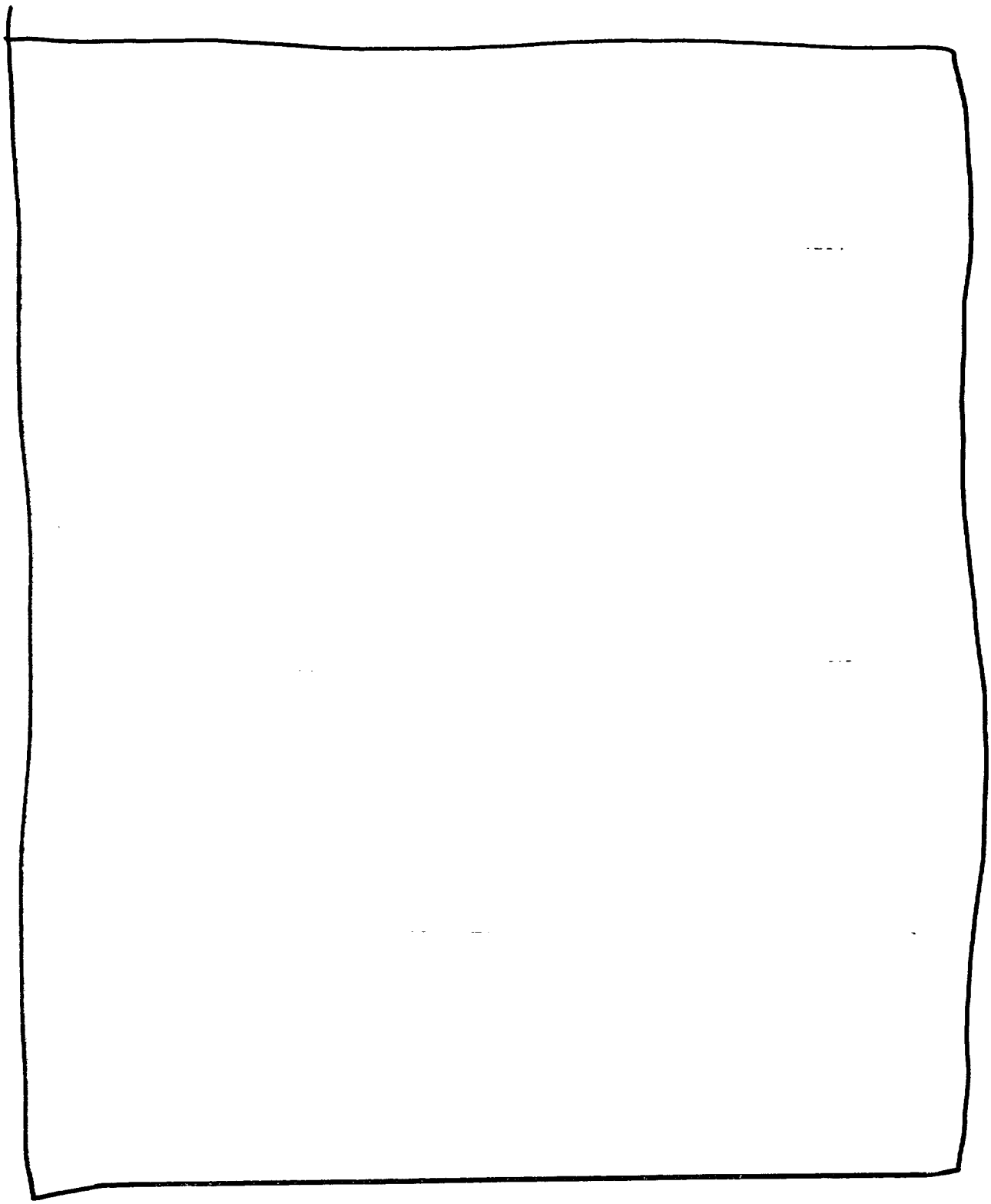
Numerous drug-drug interactions have been reported for oral contraceptives. A summary of these is found under PRECAUTIONS, Drug Interactions.

INDICATIONS AND USAGE

Estrostep is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Estrostep is indicated for the treatment of moderate acne vulgaris in females, ≥15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medications. [redacted] **ESTROSTEP should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control and plans to stay on it for at least 6 months.**

Oral contraceptives are highly effective for [redacted] Table II lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in



ESTROSTEP was evaluated for the treatment of acne vulgaris in two randomized, double blind, placebo-controlled, multicenter, Phase 3, [redacted] A total of 295 patients received ESTROSTEP and 296 received placebo. Mean age at enrollment for both groups was 24 years. At six months each study demonstrated a statistically

significant difference between ESTROSTEP and placebo for mean change from baseline in lesion counts.

Each study also demonstrated overall treatment success in the investigator's global evaluation.

Table 3. Acne Vulgaris Indication
Pooled Data 376-403 and 376-

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebral vascular or coronary artery disease
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use

- Hepatic adenomas or carcinomas
- Known or suspected pregnancy

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity, and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a *ratio* of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from References 8 and 9 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

1. Thromboembolic Disorders and Other Vascular Problems

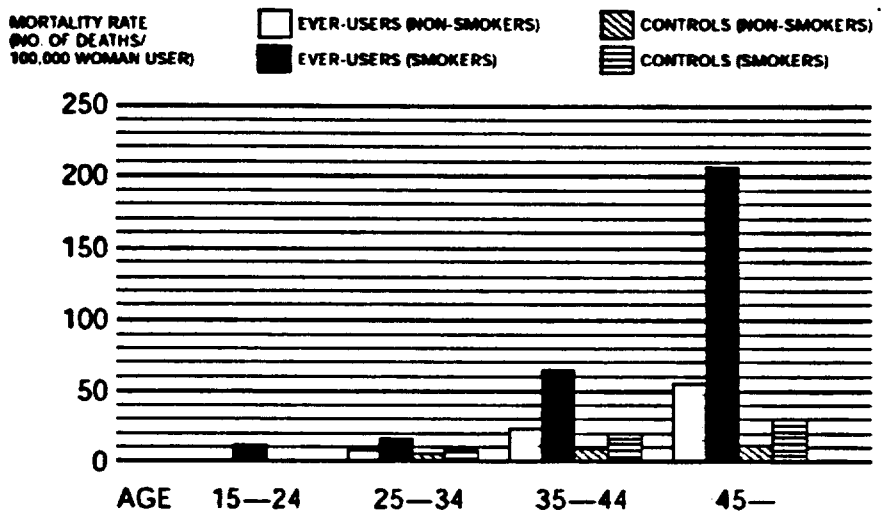
a. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six [redacted] The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking

accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 among women who use oral contraceptives.

CIRCULATORY DISEASE MORTALITY RATES PER 100,000 WOMAN YEARS BY AGE, SMOKING STATUS AND ORAL CONTRACEPTIVE USE



Adapted from P.M. Layde and V. Beral, Reference 18.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see Section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 to 6 weeks after delivery in women who elect not to breast feed.

c. Cerebrovascular disease

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years) hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users, and 25.7 for users with severe hypertension The attributable risk is also greater in older women

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestin and the nature of the progestin used in the contraceptives. The amount and activity of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular oral contraceptive, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest dose of estrogen which produces satisfactory results for the patient.

e. Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was

not demonstrated in other age groups [redacted] In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small [redacted] However, both studies were performed with oral contraceptive formulations containing 50 mcg or higher of estrogens.

2. Estimates of Mortality from Contraceptive Use

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table 5). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's but not reported until 1983 [redacted] However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed (Porter JB, Hunter J, Jick H, et al. Oral contraceptives and nonfatal vascular disease. Obstet Gynecol 1985;66:1-4; and Porter JB, Hershel J, Walker AM. Mortality among oral contraceptive users. Obstet Gynecol 1987;70:29-32), the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.